

or complete fasting, thus leading to a general amelioration of the diabetes (Case IV).

4. A progressive rise in the blood-sugar content, associated with a gradual fall in the alveolar carbon dioxide is indicative of impending coma (Cases I and III).

We wish to acknowledge our indebtedness to the attending physicians of the hospital for the privilege of observing some of their cases.

A FATAL CASE OF DIABETES MELLITUS ASSOCIATED WITH LARGE-CELL HYPERPLASIA.

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THE following case¹ is reported chiefly because the association of diabetes mellitus with large-cell hyperplasia has rarely been recorded. Moreover, certain histological changes to be described in this paper are believed to be an expression of a disturbance of fat metabolism, recent study of which has yielded important facts bearing, (1) upon the origin of fat under certain conditions in the spleen, liver, adrenals, lymph nodes, and bone marrow, and (2) upon the treatment of diabetes. Furthermore, the large-cell hyperplasia here described bears a certain superficial resemblance to the cellular changes in the spleen in that interesting and comparatively rare condition known as primary splenomegaly Gaucher, or Gaucher's disease, which has been believed by some, on insufficient grounds, to be a disturbance of fat metabolism.

There has been a great deal of confusion in the literature on this disease since it was first announced by Gaucher² in 1882, and a considerable number of mistaken diagnoses have been made. The following report may help to emphasize the importance of making

¹ Under the title "The Possible Association of Diabetes Mellitus and Splenohepatomegaly Gaucher," we gave a preliminary report of this case in the Proceedings of the Society for Experimental Biology and Medicine, New York, November 17, 1915. As some others have done, we depended mainly upon the histological examination of the tissues—spleen, liver, and lymph glands—in making our decision, though we recognized that the clinical history of the case did not support us. We take this opportunity to present the facts which establish the correct diagnosis. The case presents some unique points as far as the pathology in diabetes is concerned. As far as we can learn they have not been reported before in this country.

² De l'épithélioma primitif de la rate, Paris, 1882.

careful histological, polariscopic, and microchemical tests when it comes to deciding whether or not the pathology of a given spleen is that of true Gaucher's disease. (See the papers by Brill and Mandlebaum³ and Mandlebaum and Downey.^{4 5}

CASE NOTES.—S. R. J., male; white; American; aged twenty-eight years; single; civil engineer. Patient complains of weakness, excessive thirst, and frequent and copious urination, insomnia, and constipation.

In the spring of 1911 patient first noticed that he had excessive thirst and frequent urination. In the summer of 1911 sugar was found in his urine.

Previous Illness. During the preceding four years he had been working out of doors at his profession, engineering, chiefly field and irrigation work. Had enjoyed unusual health. In the year 1910 patient was struck by timber on right shoulder. This caused a slight injury, which produced a lameness lasting only for a day or two. In the year 1907 patient had a diseased lymphatic gland removed from the left inguinal region. This is thought to have been caused by an infection in the foot.

As a child the patient had slight attacks of scarlet fever, measles, and mumps, from which he made good recoveries. No history of nervous or venereal disease.

Family History. Father living at sixty-four years of age; well. Mother living at sixty-two years of age; well. Patient has two brothers, living and well. No history of diabetes among the immediate or collateral relatives.

Weight. Best weight, 145 pounds, 1909. Spring, 1912, 136 pounds. July 5, 1912, 134 pounds.

Physical Examination, July 5, 1912. Medium height. Fairly well developed. Thin panniculus. Teeth: many filled. Marked pyorrhea of molars. Tongue swollen and teeth-marked. Lungs clear; no areas of dulness; no rales. Heart normal in size and position. No bruit. Reduplication of second sound at apex on the tenth to twentieth beat. Rate in upright position, 108 per minute; horizontal, 80 per minute. Systolic blood-pressure, 110 mm. Nothing abnormal noted in the abdomen.

BLOOD EXAMINATIONS.

July 6, 1912. Total leukocytes, 6,040. Red cells, 5,420,000. Differential leukocyte count:

Large lymphocytes	4.0 per cent.
Small lymphocytes	19.0 "
Transitionals	3.0 "
Polynuclear neutrophiles	72.0 "
Polynuclear basophiles	1.0 "

³ Folia Hematologica, 1916.

⁴ Jour. AM. MED. SC., 1913, cxlvi, 863.

⁵ Johns Hopkins Hosp. Bull., 1916, xxvii, 302.

October 9, 1912. Differential count:

Large lymphocytes	7.1 per cent.
Small lymphocytes	9.8 "
Transitionals	5.3 "
Polynuclear neutrophiles	73.6 "
Polynuclear eosinophiles	1.3 "
Polynuclear basophiles	0.9 "
Large broken-down white cells	1.7 "

July 17, 1913. Differential count:

Large lymphocytes	13.4 per cent.
Small lymphocytes	1.8 "
Transitionals	1.2 "
Polynuclear neutrophiles	78.0 "
Polynuclear eosinophiles	3.6 "
Normoblasts	14.0 "

Early in the illness (September, 1912) the patient was examined in consultation by Dr. Elliot P. Joslin, who also noted nothing abnormal in the patient's abdomen. Our attention was not directed to the spleen, however, and it is not improbable that a slight enlargement of it was overlooked.

Because of the prominence of the patient and of his family, many physicians in various parts of the United States were consulted in this case. Practically every known dietary and medical treatment was employed at the suggestion of these various clinicians. The patient resided in Ithaca; the general clinical supervision of the case and the urine examinations were conducted by one of us in Rochester.

In the year 1912, when this patient was under observation, clinicians generally believed that the most important factor in the problem of diabetes was carbohydrate metabolism. The significance of fat and protein metabolism and the total caloric needs of the diabetic were not clearly understood, and were given only minor consideration. It was generally believed that a patient with diabetes must, for the maintenance of life and comparative health, have a minimum food intake of at least 30 calories per kilo of body weight. On this basis the patient, weighing approximately 134 pounds or 61 kilos, would have required daily at least 1830 calories while at rest and at least 15 per cent. more, or approximately 2200 calories, while undergoing moderate exercise.

The clinical experience of one of us (Williams) during the past year, in which more than 50 cases have been accurately studied with reference to this point as result of the epoch-making work of Allen in the Rockefeller Institute, demonstrates that patients can live in comparatively good health on total food intakes far below these minimum standards which had hitherto been thought necessary.

Furthermore, recent clinical experience has shown that the feeding of the average diabetic beyond this formerly supposed normal minimum requirement of 30 calories per kilo of body weight will

TABLE I.—SHOWING URINE EXAMINATION AND FOOD INTAKE ON VARIOUS DAYS THROUGHOUT TREATMENT.

Date.	Urine.			Total NH ₃ (Folin).	Sugar (polar).	Diet.				
	Volume.	Specific gravity.	Diabetic acid.			Carbohydrate.	Protein.	Fat.	Alcohol.	Calories.
1912										
July 5	1200	1023	++	1.9	48	20	100	200	0	2310
6	960	1026	++	2.1	27	65	100	200	0	2500
27	2490	1023	+	0.6	30	90	33	74	0	905
Aug. 8	2660	1030	++	2.7	86	190	75	200	0	3000 +
Oct. 20	2040	1031	+	0.6	45	64	75	30	12	1010
31	2460	1026	0	0.3	38	45	75	30	12	949
Nov. 12	2160	1025	0	0.5	56	56	75	30	12	878
1913										
Jan. 28	4080	1031	+++	2.6	122	35	100	200	0	2370
Feb. 2	3630	1033	+++	3.0	152	66	90	200	0	2450
June 12	3600	1030	++++	4.1	108	90	100	200	0	2640
July 27	3630	1030	++++	4.4	123	200	150	180 +	0	3000
31	3930	1027	++++	3.3	172	200	150	180 +	0	3000

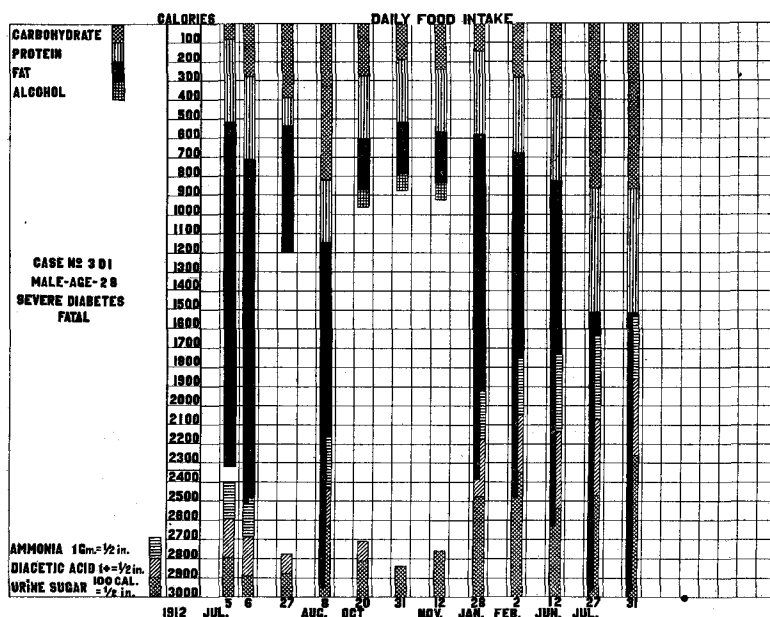
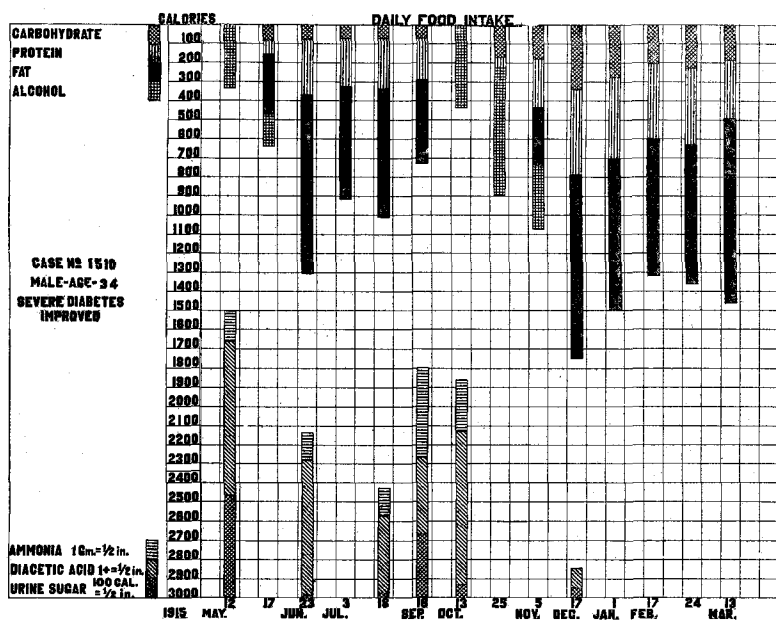


CHART I. Plotted from Table I.—Showing graphically the relation between the food intake and urine outgo. Food intake for each day reads from above down in calories. The urine examinations read from the bottom up as shown by key at end of chart. It will be noted that on days when much food was fed, particularly fat, the acidosis as measured by the ammonia and diacetic acid excretion was worse. On August 8 the patient was given an oatmeal diet. The various diets shown in this chart represent the culminations of various dietary procedures.

precipitate in the majority of cases of advanced diabetes both glycosuria and acidosis; and if, as was formerly taught, the patient be fed much in excess of this so-called standard, not only will his tolerance for carbohydrate be seriously impaired but his acidosis will be proportionately increased. This fact is illustrated by Table I and Chart I.

In a study of this table it will be observed that on those days when the patient was fed a diet low in fat the severity of his acidosis, as measured by the ammonia output, declined. It is altogether probable that had this dietary procedure been pursued further the diabetic condition would have been ameliorated, for when it was thought desirable to restore the losing weight of the patient and apparent weakness by feeding the patient large amounts of fat his acidosis increased in severity. This is the justification for the belief, from a clinical stand-point, that the patient had a serious failure in fat metabolism.



Because of this erroneous belief about the normal minimum food requirement, and because of the then current clinical teaching, in effect that fat should constitute the major portion of a diabetic's diet, this patient was fed fat in considerable amounts, as indicated in Table I and Chart I.

To contrast the effects of high and low fat content in the diet in severe diabetes we insert a graphic record (Chart II) of a case now under treatment. Table II gives dietetic and other details. It will be observed that the cholesterol content of this patient's blood has been very high. The presence of this substance in the tissues and certain of its experimental effects will be discussed later.

TABLE II.

Blood removed.	Diet previous twenty-four hours.				Urine sugar.	Free ammonia.	CO ₂ in lung air, mm.	Cholesterol per 100 c.c. blood, mg.
	Carbohydrate.	Protein.	Fat.	Calories.				
1916								
Mar. 14	44	69	108	1428	0	0	36.2	510 ⁶
April 10	43	71	88	1258	40	0.82	41.2	428
May 11	33	84	96	1363	..	..	30.0	833
15	61	35	21	674	101	2.81	31.4	717
23	No food	15 hours previous			19	1.21	39.3	833

Returning to the case under discussion, we may say that there was nothing unusual in the general course of the disease. It progressed steadily and the patient died in coma August 1, 1913.

Postmortem Examination. Body was embalmed one hour after death. The fluid used contained about 7 per cent. of formalin and a small amount of carbolic acid. Postmortem was held twelve hours after death, the object at the time being mainly to secure the pancreas. Abdominal organs only were examined.

Macroscopic findings: All organs had a normal appearance except the spleen, which was somewhat enlarged. It weighed 330 gms. Shape not unusual; dimensions: 13 x 10.5 x 6 cm. Color normal, both superficially and when sectioned. No amyloid areas.

*Microscopic examination:*⁷ Pancreas, liver, spleen, kidneys, adrenals, and lymph glands were sectioned. Specimens were fixed in formalin, Zenker's fluid, and osmic acid.

Kidneys normal.

Pancreas: No generalized increase in connective tissue, but some

⁶ Cholesterol estimation was made by Prof. W. R. Bloor, whose method (Jour. Biol. Chem., 1916, xxiv, 227) is employed in the tests. Normal blood contains between 170 and 240 mg. cholesterol per 100 c.c.

⁷ Specimens of the spleen and pancreas were examined by Drs. L. Hektoen, James T. Ewing, E. L. Opie, and A. S. Warthin, to whom we desire to express our thanks for valuable reports and suggestions.

indication of atrophy, with duct stasis. Few areas of strongly acidophile alveoli. Islets normal in number and distribution. Some islets enlarged, in few instances to twice ordinary size. No marked abnormality of structure shown, but there was a tendency to hypertrophy and to contain hyperchromatic nuclei. Islet cells closely packed together, and difficult to distinguish, with cell masses separated by conspicuous capillaries, walls of which appeared somewhat thickened. Slight sclerosis. No evidence of hyaline change in islet epithelium (see Fig. 1).

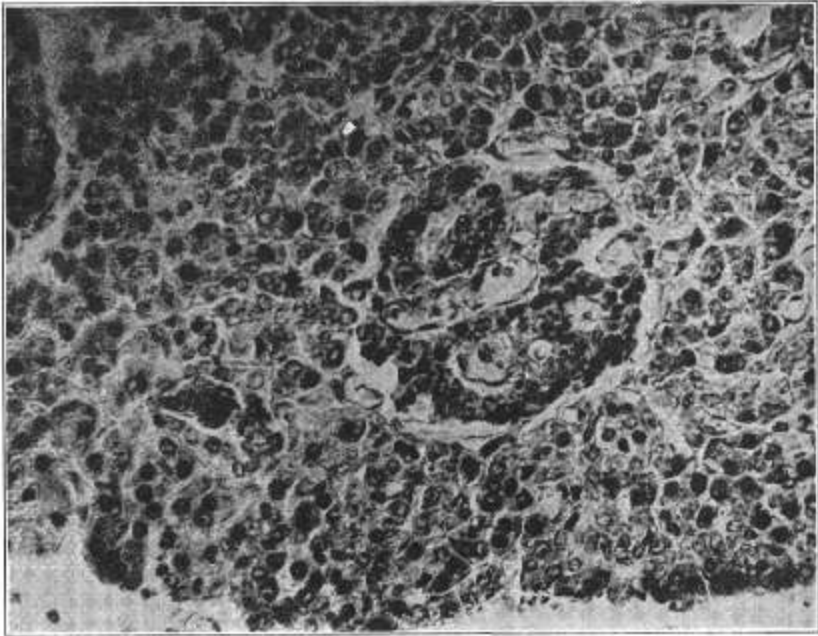


FIG. 1.—Section of the pancreas, showing a single islet. Zenker fixation. Iron hematoxylin. $\times 400$.

Spleen: The spleen throughout contained numerous large cells. These cells were mostly round or oval, and were of varied size. They were especially abundant in the pulp, but some could be seen to penetrate into the periphery of the nodules. Nodules otherwise were normal. Scarcely any sclerosis. No giant cells noted. Further description given below (see Fig. 2).

Lymph glands: Two lymph glands from the duodenal mesentery were sectioned. They showed the same large cells as did the spleen, though the cells were smaller and not so plentiful as in the spleen. No pigment was present (see Fig. 3).

Liver: A few cells bearing superficial resemblance to those in the spleen were found in the liver sinusoids; not more than three or

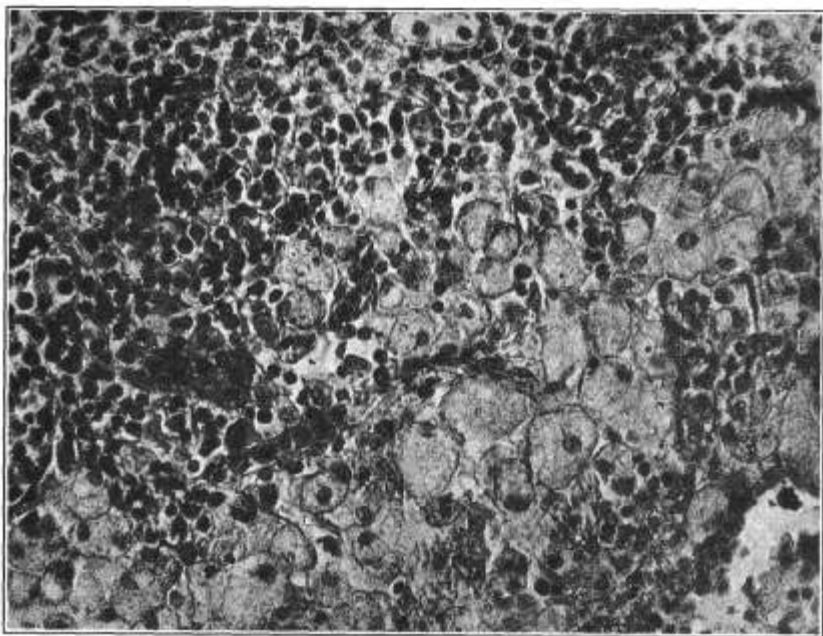


FIG. 2.—Section of the spleen, showing large-cell hyperplasia. Zenker. Hematoxylin and eosin. $\times$ ca. 350.

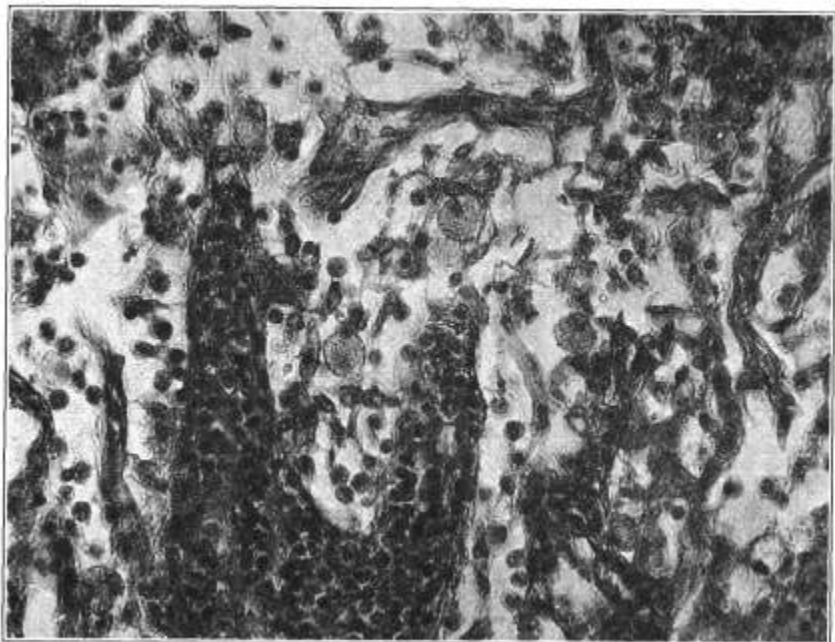


FIG. 3.—Section of a mesenteric lymph gland. A few large hyperplasia cells are seen about the middle of the section. Zenker. Hematoxylin and eosin. $\times$ ca. 350.

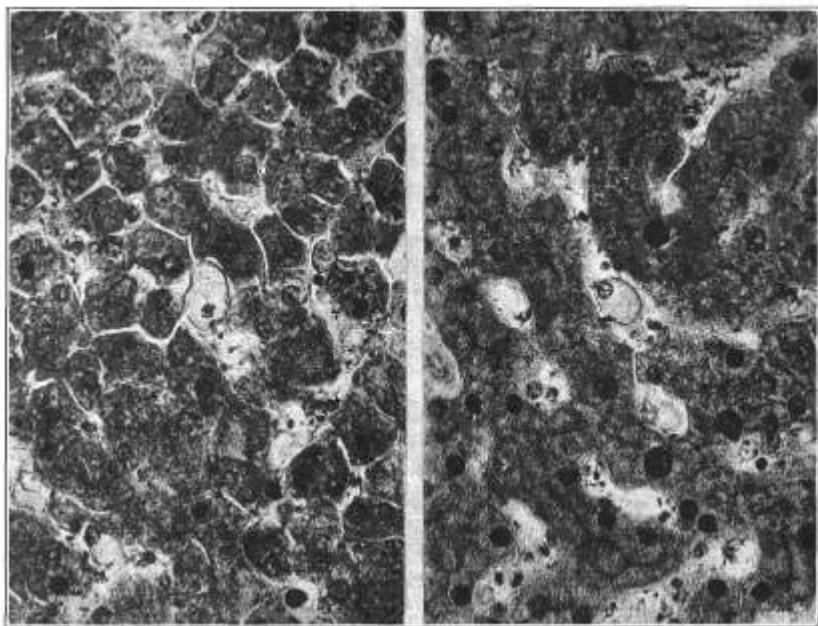


FIG. 4.—Two sections of liver. In the middle of each section may be seen a single Kupfer cell, located in a sinusoid. See text for description. Formalin. Iron-hematoxylin. $\times 350$.

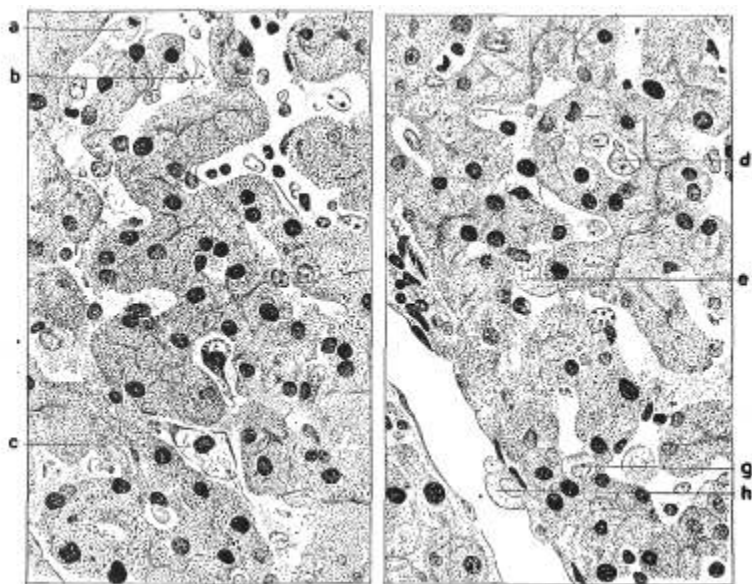


FIG. 5.—Microprojection drawing of two liver sections. Kupfer cells are seen at *a*, *b*, *c*, *d*, *e*. At a large cell which apparently has wandered into a vein is marked. $\times 400$.

four generally were seen in a lobule, though occasionally they were fairly numerous (see Figs. 4 and 5).

Further details about the liver and adrenal glands are given in the following comments, which were made, in a personal communication to the authors, by Dr. Frank S. Mandlebaum,⁸ who kindly examined the tissues:

"It cannot be denied that the large cells in the spleen have a certain resemblance to the large cells of Gaucher's disease, but pictures of this kind are found in a variety of pathological processes. The cells in your cases are more rounded in outline than those of Gaucher's disease, the characteristic wrinkled and streaked appearance of the cytoplasm is missing, and the impression is obtained that some substance originally contained in the cells has been dissolved out in the process of hardening and embedding. Furthermore, dilated venous sinuses filled with blood and large cells are not prominent. The sections of the liver do not in any way resemble those of Gaucher's disease, even though some large cells are present in the sinusoids. The lesion is a granular degeneration with hypertrophy of the stellate cells of Kupfer (see Figs. 4 and 5), with secondary proliferation and desquamation. Some of these cells may have been carried to the liver from the spleen through the portal circulation. The lesion in the lymph node is a marked hyperplasia of the cellular reticulum such as is frequently found in many pathological processes, but bears no resemblance whatever to the lesion of Gaucher's disease.

"Examination of the blocks of tissue of the spleen and liver reveal the true nature of the pathological process. Fortunately the tissues were fixed and preserved in formalin, therefore the substance in the large cells can be identified. Frozen sections of the spleen stained with Sudan III and Nile blue show the presence in the large cells of a considerable amount of neutral fat and lipoids. The polariscope shows anisotropic bodies which disappear on heating and reappear on cooling, thus proving the presence of cholesterin esters. Polariscopic examination of liver sections stained with Nile blue shows that the cholesterin esters are present in the stellate cells of Kupfer. Unfortunately no material from the lymph nodes is available, therefore lipid tests cannot be made. I feel, however, that the large swollen reticular cells in the lymph nodes would show the same microchemical and polariscopic reactions.

"Although the histological picture in your case is sufficient proof that this is not an instance of Gaucher's disease, the simple presence of fat and lipoids in the large cells is positive evidence that the case does not belong to this group, for these substances have never been found in any of the authentic cases. I might also say that the clinical history of the case, as published in your preliminary

⁸ This case is the one referred to by Drs. Mandlebaum and Downey in their paper in the *Johns Hopkins Hosp. Bull.*, April, 1916, vol. xxvii, No. 302.

report, together with the autopsy findings, are not suggestive of Gaucher's disease.

"I have no hesitancy, therefore, in stating that your case is one of lipid deposits in the spleen and other organs, due to diabetes with a probable lipoidemia."

In a later letter Dr. Mandlebaum wrote to us concerning the adrenals as follows:

"Polariscopic examination of frozen unstained sections of the adrenal shows an appreciable increase of double refracting substances, especially confined to the zona glomerulosa and zona reticulosa, with some infiltration of the zona fasciculata as well. These substances disappear on heating and reappear on cooling. When frozen sections are stained with Nile blue a confirmation of the above findings is obtained. With Sudan III the cells of the zona glomerulosa are filled with bright yellow droplets. The cells of the zona fasciculosa appear enlarged, with the yellow droplets at the periphery of the cells and in the cells in the walls of the capillaries. The cells of the zona reticulosa are more completely filled with these droplets. Several small islands of cortical cells are found in the medullary portion of the gland, giving typical reactions with Nile blue and Sudan III.

"Treating sections of the adrenal with alcohol causes a complete disappearance of the anisotropic bodies, and upon subsequent staining with Nile blue and Sudan III no reactions for lipoids are obtained.

"Paraffin sections stained with hematoxylin and with Van Gieson show hypertrophy of the cells of the zona glomerulosa. These cells are increased in number and in size, and some have undergone granular degeneration. The hypertrophy of the cells is even more marked in the zona fasciculata and corresponds to the lipid infiltration produced experimentally in rabbits and guinea-pigs by feeding with cholesterol (Antschow). The findings in the adrenal are still further proof of the probable lipoidemia in your case."

A fact worthy of note in this case is the absence of evidence of malfunctioning islets in the pancreas. Other instances of this sort are well known. On the other hand, degenerative changes in the islets have frequently been seen in diabetes, both in the human subject and in experimental animals. The amount of islet tissue necessary doubtless varies in different animals. In unpublished experiments by one of us in Ithaca with Dr. C. W. Webb, of Clifton Springs, N. Y., we have been astonished to see several dogs live a number of weeks with an extraordinary small amount of islet tissue. One dog had the head of the pancreas removed and the distal duct tied. He lived six months, free from glycosuria as long as he was given meat only, on which diet his weight decreased from 11 kg. to 5.5 kg. He developed distemper and was killed. We could find nothing but a strand of connective tissue one inch long repre-

senting the part of the pancreas left in the animal, and no islet cells could be identified.

CONCERNING THE LIPOIDS. Lipoidemia has long been known to be present in diabetes (see Kusunoki⁹ for index to literature), and there is reason to suspect that it occurs frequently in advanced or serious cases. One of us (Williams) in a recent, not yet reported, study of 22 cases of advanced diabetes found the cholesterin content of the blood increased in 16 cases. We find in the literature, however, very few cases of diabetes that resemble ours in histopathology. As Anitschow¹⁰ says, it is very desirable that such cases be reported. The first instance of large-cell hyperplasia in this disease which we have found was given by Schultze,¹¹ who, according to Anitschow,¹² would be entitled to priority in the matter. Schultze regarded the large cells of the spleen in his case as probably identical with those in Gaucher's disease. In this he was doubtless mistaken, for, according to modern views (see Mandlebaum and Downey^{13 14}), these large cells in Gaucher's disease contain no lipoids. They were present in Schultze's case in large amount, and there was marked lipoidemia.

Later, Lutz¹⁵ described 2 cases of lipoidemia in diabetes with similar hyperplasia of the spleen. The cells contained isotropic fat, mostly, but there was some in the anisotropic form. Although Lutz notes the marked similarity of the microscopic picture in his cases with that in Gaucher's disease, he did not claim that the pathological processes were identical. In the cases of Schultze and Lutz the liver, adrenals, and bone marrow were not said to be involved, though the lymph nodules were found by Lutz to contain large cells infiltrated with fat. They appeared to be desquamated endothelial cells.

These facts are enhanced in interest and importance when taken in connection with the effects of hypercholesterolemia, as reported by Anitschow, Chalatow, Krylow, Rothschild, Sternberg, Landau and McNee, Soper in Ziegler's *Beitr. z. path. Anat. u. allg. Path.*, 1913 and 1914, and by Adler,¹⁶ Bailey,¹⁷ Borberg¹⁸ and others. While we cannot give an analysis of the literature in this article, we may state briefly that it has been shown by feeding animals with cholesterin for several months that a hyperplasia, with lipoid infiltration, can be produced in the spleen and bone marrow. The spleen hyperplasia is strikingly similar to that seen in the case of

⁹ Ziegler's *Beitr. z. path. Anat. u. z. allg. Path.*, 1914, lix, 564.

¹⁰ *Ibid.*, 1913-1914, lvii, 201.

¹¹ *Verhandl. d. deutsch. path. Gesellsch.*, Strassburg 15 Tagung, 1912.

¹² *Loc. cit.*

¹³ *Loc. cit.*

¹⁴ Ziegler's *Beiträge*, 1914, lviii, 273.

¹⁵ *Jour. Exp. Med.*, 1914, vol. xx.

¹⁷ *Ibid.*, 1916, xxiii, 69.

¹⁸ *Skand. Arch. f. Physiol.*, 1914, xxxii, 287.

¹⁴ *Loc. cit.*

diabetes which we have described in this paper. (Presumably the bone marrow in our own case would have shown the same pathological feature, but unfortunately we did not take a sample of the marrow, as we had no suspicion of hyperplastic change at the time the tissues were fixed.) Other interesting results of these experiments, such as atheromatous conditions of the aorta, were obtained by Anitschow and others. For these details the reader is referred to the papers above cited.

On the chemical side numerous studies are available in the works of the several authors mentioned above. From these investigations one sees that the tendency is more and more not to regard the regulation of the lipid supply of the body as the function of any one organ, as, for instance, the liver, which has received so much attention in former years. It appears that the spleen, adrenals, and bone marrow, as well as the liver, play an important part; whether jointly or separately is not yet clear. Aside from its digestive function the pancreas may also contribute in some way. Aschoff has become so convinced of the interrelation of these organs that he regards certain endothelial structures in the bone marrow, spleen, and lymph nodes, and the stellate cells of Kupfer in the liver, together with the adrenal cortex, as the "endothelial metabolism apparatus," the conception being that it, as well as other tissues of the body, is concerned with the intermediate metabolism of cholesterin (Landau¹⁹). English authors, *e. g.*, Dorie, Ellis, Fraser and Gardner,²⁰ believe that a "cholesterin balance can be maintained in the body by the food intake." Certain French writers (Chauffard and others) think that the adrenals secrete cholesterin (see Rothschild²¹). They stand practically alone in this view. (For recent discussion of the subject see Rothschild's papers²²). Ciaccio²³ lays stress on the apparent relations of the lipoids, phosphatids, cholin, and glycerin esters. He thinks they have a complex history in the adrenals and other organs.

Another statement bearing on the question of fat metabolism may be made in this connection. In regard to the causes of fatty infiltration (and degeneration), Fischer and Hooker²⁴ make an attractive suggestion in a recent article on the physical chemistry of emulsions. They hold that an important factor in the stabilizing of an emulsion is the state of the colloid that may be the emulsifying agent. A fat emulsified in a hydrated colloid may be made to separate out by altering the hydration capacity of the colloid by acids, or, in some instances, by alkalies. Fischer and Hooker believe that fat in tissue

¹⁹ Ziegler's Beiträge, 1914, lvi, 667.

²⁰ Proc. Roy. Soc. (Biology) London, 1908, pp. 212, 227; 1908, pp. 109, 129, 230, 505; 1910, p. 559; 1912, p. 461.

²¹ Ziegler's Beiträge, 1914, lx, 39.

²² Ziegler's Beiträge, 1914, vol. lx.

²³ Arch. f. exp. Pathol. u. Pharmacol., 1915, lxxviii, 347.

²⁴ Science, 1916, N. S., xliii, 468.

cells is thus emulsified, and that it may appear in visible form when the hydration capacity of the tissue colloids is decreased. Hence, according to this view, a fatty infiltration may have an entirely different cause from those ordinarily offered. Might not the acidosis of diabetes favor this phenomenon of the appearance of lipoids in the tissue cells and blood in this disease?

In conclusion, one sees there is a tendency on the part of not a few writers to build up a polyglandular theory of fat metabolism similar to that proposed by von Noorden and others to explain the control of the carbohydrates in the body. This theory regarding the carbohydrates and the origin of diabetes has been somewhat discredited by Minkowski, Opie, and Allen.²⁵ Nevertheless, a close correlation of organs by hormones or other bodies is a fundamental point in physiology, and one to be taken into account, along with other factors in considering any disorder of metabolism.

The whole question of fat metabolism is in need of much further study, which must not overlook the importance of the carbohydrates, for, as Bloor²⁶ states in a recent contribution to the subject of fat assimilation, sugar appears to be necessary in some stage for complete combustion in the oxidation of fats.

From studies, with the more refined technic of the present day, we may expect to see rapid progress toward a clear understanding of the etiology and pathology of diabetes.

SUMMARY. A case of fatal diabetes with large-cell hyperplasia of the spleen, lymph nodes, and liver is presented. It is the fourth case on record so far as the authors can tell. Other cases have doubtless occurred, but the hyperplasia has been overlooked. It is highly desirable, therefore, that thorough autopsies be made whenever possible. The spleen, lymph nodes, adrenals, liver, and bone marrow especially should be examined, microscopically and with the polariscope, to determine the nature of the cell contents.

The hyperplasia in the case described, and in the other cases reported, has some resemblance to the cell changes in Gaucher's disease of the spleen. In this disease lipoids are absent in the large cells, which, furthermore, have characteristic histological features. Moreover, Gaucher's disease is a familial disorder.

It is shown that overfeeding with fat increases acidosis in diabetes and probably bears some relation, as yet not understood, to lipoidemia. The acidosis is readily controlled, as Allen and Joslin have shown.

A brief discussion of some of the newer ideas regarding fat metabolism is given.

We wish to make acknowledgments to Professors B. F. Kingsbury and S. H. Gage for assistance with the photographs.

²⁵ Glycosuria and Diabetes, 1913, p. 842.

²⁶ Jour. Biol. Chem., 1916, xxiv, 447.